This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-19. (Canceled)

20. (Currently Amended) A ~~β sheet multimeric~~ TRAIL cytokine with selectivity for a target receptor, in which one or more amino acids in the cytokine that are located in the receptor-binding interface are substituted for replacement residues that include amino acid side-chain conformations that are predicted to fit into the binding interface with the target receptor so as to provide an increase in binding affinity and selectivity/specificity of the cytokine protein for that target receptor, provided that these are not residues interacting with amino acids that are conserved among receptors bound by the cytokine protein, wherein said cytokine has the amino acid sequence of SEQ ID NO: 1, except that it is mutated at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 to an amino acid other than alanine.

21. (Currently Amended) ~~A β sheet multimeric~~ The TRAIL cytokine according to claim 20 which has altered affinity for a particular target receptor.

22. (Currently Amended) A ~~β sheet multimeric~~ TRAIL cytokine with selectivity for two or more target receptors wherein selectivity for a first target receptor is achieved by substituting one or more amino acids in the cytokine for replacement residues so as to decrease affinity for one or more different target receptors, provided that these are not residues interacting with amino acids that are conserved among receptors bound by the cytokine protein, wherein said cytokine has the amino acid sequence of SEQ ID NO: 1, except that it is mutated at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 to an amino acid residue other than alanine.

23. (Currently Amended) A cytokine according to claim 20, which is further mutated at one or more of the positions ~~131,~~ 269, ~~130, 160, 218, 220, 149, 155, 214, 195,~~ 191 and 267 in the cytokine.

24. (Canceled)

25. (Canceled)

26. (Currently Amended) ~~A~~ The TRAIL cytokine according to claim 20 [[25]], which has superior selectivity for the DR5 (TRAIL-R2) or DR4 (TRAIL-R1) over the decoy receptors DcR1 (TRAIL-R3) and DcR2 (TRAIL-R4).

27. (Currently Amended) ~~A~~ The TRAIL cytokine according to claim 20 [[25]], which has superior selectivity for the death receptor 5 (TRAIL-R2) over selectivity for the death receptor 4 (TRAIL-R1).

28. (Currently Amended) ~~A~~ The TRAIL cytokine according to claim 26, which contains one or more of the mutations G131R, ~~D269H, D269K, D269R,~~ R130E, G160K, D218R, G160M, I220M, I220H, R149D, R149H, ~~E155M~~, T214R, and E195R, ~~R191E and D267R~~.

29 – 32. (Canceled)

33. (Currently Amended) ~~A~~ The TRAIL cytokine according to claim 20 [[25]], which has superior selectivity for the death receptor 4 (TRAIL-R1) over selectivity for the death receptor 5 (TRAIL-R2).

34. (Currently Amended) ~~A~~ The TRAIL cytokine according to claim 33, which contains one or more of the mutations D218Y, D218E, D218K, D218H and D218F ~~D21E8F~~.

35. (Currently Amended) A β sheet multimeric- TRAIL cytokine having the amino acid sequence of SEQ ID NO: 1 with selectivity for a target receptor, wherein the TRAIL cytokine ~~whose~~ sequence has been altered by;

a) mutating a residue in a monomer component of the multimeric cytokine protein so as to improve the free energy of the monomer of the multimeric complex relative to the wild-type unmutated monomer component, wherein said mutated residue is non-

conserved between homologous members of the cytokine family, so as to be more stable than the wild-type, unaltered cytokine protein, and

b) substituting one or more amino acids in the cytokine that are located in the receptor-binding interface for replacement residues that include amino acid side-chain conformations that are predicted to fit into the binding interface with the target receptor so as to provide an increase in binding affinity and selectivity/specificity of the cytokine protein for that target receptor, provided that these are not residues interacting with amino acids that are conserved among receptors bound by the cytokine protein, so as to provide variants with enhanced stability and increased binding affinity and selectivity/specificity for the target receptor, and wherein said cytokine is mutated at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 of the amino acid sequence of SEQ ID NO: 1 to an amino acid residue other than alanine.

36. (Currently Amended) A β sheet multimeric TRAIL cytokine having the amino acid sequence of SEQ ID NO: 1 cytokine with selectivity for a target receptor, wherein the TRAIL cytokine ~~whose~~ sequence has been altered by;

a) mutating a residue in a monomer component of the multimeric cytokine protein so as to improve the free energy of the monomer or of the multimeric complex relative to the wild-type unmutated monomer component, wherein said mutated residue is non-conserved between homologous members of the cytokine family, so as to be more stable than the wild-type, unaltered cytokine protein, and

b) substituting one or more amino acids in the cytokine for replacement residues so as to decrease affinity for one or more different target receptors, provided that these are not residues interacting with amino acids that are conserved among receptors bound by the cytokine protein so as to provide variants with enhanced stability and selectivity/specificity for the target receptor, and wherein said cytokine is mutated at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 of the amino acid sequence of SEQ ID NO: 1 to an amino acid residue other than alanine.

37 – 52. (Canceled)

53. (Currently Amended) A method for the alteration of the selectivity of a ~~β-sheet multimeric~~ TRAIL cytokine having the amino acid sequence of SEQ ID NO: 1 for a target receptor, the method comprising

a) identifying amino acids in the cytokine that are located in the receptor-binding interface as candidates for mutation;

b) discarding residues interacting with amino acids that are conserved among receptors bound by the cytokine protein;

c) discarding residues interacting with the receptor backbone; and

d) substituting each of one or more residues in the cytokine protein for replacement residues that include amino acid side-chain conformations that are predicted to fit into the binding interface with the target receptor so as to provide an increase in binding affinity and selectivity/specificity of the cytokine protein for that target receptor, and wherein said cytokine is mutated at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 to an amino acid residue other than alanine.

54. (Currently Amended) A ~~β-sheet multimeric~~ TRAIL cytokine whose sequence has been altered by a method according to claim 53 so as to alter its affinity for a particular target receptor.

55 – 57. (Canceled)

58. (Currently Amended) The ~~A~~ cytokine according to claim 54 [[57]], which has superior selectivity for the DR5 (TRAIL-R2) or DR4 (TRAIL-R1) over the decoy receptors DcR1 (TRAIL-R3) and DcR2 (TRAIL-R4).

59. (Currently Amended) The ~~A~~ cytokine according to claim 54 [[57]], which has superior selectivity for the death receptor 5 (TRAIL-R2) over selectivity for the death receptor 4 (TRAIL-R1).

60. (Currently Amended) The ~~A~~ cytokine according to claim 58, which contains one or more of the mutations G131R, ~~D269H, D269K, D269R,~~ R130E, G160K, D218R, G160M, ~~D218Y, D218E, D218K, D218H,~~ I220M, I220H, R149D, R149H, D218F, ~~E155M~~, T214R, and E195R~~, R191E and D267R~~.

61. (Currently Amended) The ~~A~~ cytokine according to claim 60, which contains the mutations G160M and D269H.

62. (Currently Amended) A method for obtaining variants of a β sheet multimeric TRAIL cytokine having the amino acid sequence of SEQ ID NO:1 with enhanced stability and increased binding affinity and selectivity/specificity for a target receptor comprising the steps of:

a) mutating a residue in a monomer component of the multimeric cytokine protein so as to improve the free energy of the monomer or of the multimeric complex relative to the wild-type unmutated monomer component, wherein said mutated residue is non-conserved between homologous members of the cytokine family, and

b) identifying amino acids in the cytokine that are located in the receptor-binding interface as candidates for mutation, discarding residues interacting with amino acids that are conserved among receptors bound by the cytokine protein, discarding residues interacting with the receptor backbone; and substituting each of one or more residues in the cytokine protein for replacement residues that include amino acid side-chain conformations that are predicted to fit into the binding interface with the target receptor, and wherein said cytokine is mutated at one or more amino acid positions of 130, 131, 149, 160, 195, 214, 218, and 220 to an amino acid residue other than alanine.

63 – 68. (Canceled)

69. (Currently Amended) A cytokine according to claim 27, which contains one or more of the mutations G131R, ~~D269H, D269K, D269R,~~ R130E, G160K, D218R, G160M, I220M, I220H, R149D, R149H, ~~E155M,~~ T214R, and E195R~~, R191E and D267R~~.

70 – 71. (Canceled)

72. (Currently Amended) A TRAIL cytokine according to claim 59, which contains one or more of the mutations G131R, ~~D269H, D269K, D269R,~~ R130E, G160K, D218R, G160M, ~~D218Y, D218E, D218K, D218H,~~ I220M, I220H, R149D, R149H, ~~D218F, E155M~~, T214R, and E195R~~, R191E and D267R~~.

73. (New) A TRAIL cytokine according to any one of claims 20-22, 26-28, or 33 further comprising a mutation at position 269.

74. (New) A TRAIL cytokine according to claim 73, which contains one of the mutations D269H, D269K, and D269R.

75. (New) A TRAIL cytokine according to claim 35 or 36 further comprising a mutation at position 269.

76. (New) A TRAIL cytokine according to claim 75, which contains one of the mutations D269H, D269K, and D269R.

77. (New) A TRAIL cytokine according to claim 53 further comprising a mutation at position 269.

78. (New) A TRAIL cytokine according to claim 77, which contains one of the mutations D269H, D269K, and D269R.

79. (New) A TRAIL cytokine according to claim 74, which contains the mutations G160M or D269H.

80. (New) A TRAIL cytokine according to claim 74, which contains the mutations D269H and T214R.

81. (New) A TRAIL cytokine according to claim 74, which contains the mutations D269H and E195R.

82. (New) A TRAIL cytokine according to claim 76, which contains the mutations D269H and T214R.

83. (New) A TRAIL cytokine according to claim 76, which contains the mutations D269H, E194I and I196S.

84. (New) A method of treating cancer by exposure of cancer cells to a DR4-specific TRAIL variant according to claim 20 or 22, in combination with cytotoxic therapies such as ionising radiation and chemotherapy.

85. (New) A method of treating cancer by exposure of cancer cells to DR5-specific TRAIL variant according to claim 20 or 22, in combination with cytotoxic therapies such as ionising radiation and chemotherapy.